THE ETIOLOGY OF BLACKWATER FEVER

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Marchiafava and Bignami (1894), in referring to malarial poisoning, say: 'We may mention those morbid states which are developed after the malarial (parasitic) infection has passed away; for instance, the post-malarial fevers, the delirium, the post-malarial haemoglobinuria.' Mannaberg (1894) emphasises the fact that Kelsch and Kiener proved that in every severe case of malaria, even in every malarial cachexia, haemoglobinuria may be observed, and calls attention to the effects of lesions of the renal epithelium as pointed out by Bignami. These observers recognised haemoglobinuria as a relatively common complication or sequela of malaria, and it is of interest that they recognised it as a fact that, when haemoglobinuria develops after malaria, the parasites have disappeared from the peripheral blood.

Later quinine was added as a supplementary cause of the attacks of haemoglobinuria. Of the numerous more recent theories of the cause of blackwater fever with which we are chiefly concerned here, the first is Manson's, who stated that blackwater fever is a disease by itself, separate from and not dependent upon malaria; the second, which is an advance on this, claims for blackwater fever that it is produced by a living organism. Further suggestions, still largely in the realm of speculation, have been made by which this or that form of parasite is stated to be the cause of blackwater fever. Some of these parasitic theories we shall have the opportunity of mentioning later.

Although it is thirty years ago since Manson promulgated the theory that blackwater fever is a disease entity, and although numerous observers since have attributed to different organisms the

credit of being the cause of it, the specific parasite which gives rise to blackwater fever is still undiscovered. The older malaria, malaria-quinine and similar theories have suffered much at the hands of critics, but to fill their place little of definite value has been produced. The tendency has been to admit that while haemoglobinuria occurs as the result of malaria, and quinine and other drugs, yet apart from these haemoglobinurias, and separable from them even when, in the tropics, they occur in chronic malaria cases who have been taking quinine, there is a definite recognisable condition of haemoglobinuria which constitutes the main sign of blackwater fever.

Castellani and Chalmers (1919) differentiate the haemoglobinurias which may occur in the tropics into three groups: Symptomatic, Toxic and Specific. Under symptomatic they put haemoglobinuria occurring in the course of malaria, Raynaud's disease, acute specific fevers, and after severe burns. The toxic group includes haemoglobinuria resulting from the administration of quinine and its salts, chlorate of potash, antipyrin, carbolic acid, and naphthol, or from vegetable substances such as *Vicia faba*. The specific group comprises blackwater fever and paroxysmal haemoglobinuria. At first glance such a classification appears of assistance to those who are likely to come in contact clinically with blackwater fever cases, eliminating from the sphere of blackwater fever those confusing elements which are introduced if what is in reality a symptomatic or toxic haemoglobinuria is erroneously attributed to a specific disease.

Before accepting this classification, however, it may be well to consider in some detail the signs and symptoms by which these varieties of haemoglobinuria are said to be distinguished from one another. In Table I, compiled from these authors, are given in comparative columns the signs and symptoms under each form of haemoglobinuria, the symptomatic group being represented by malaria, the toxic by quinine, and the specific by blackwater fever.

Reviewing the table, it is worthy of note that the signs and symptoms of quinine haemoglobinuria resemble those of an attack of blackwater fever but are not so severe, and that jaundice is specially mentioned as being slight or absent in the former condition. The malaria group is allotted six positive signs and symptoms, which

TABLE I

Comparison of signs and symptoms of Tropical Haemoglobinurias.

Symptomatic	Toxic	Specific
Haemoglobinuria in malaria, Raynaud's Disease, Acute Specific Fevers and after severe Burns	Haemoglobinuria caused by Quinine, Chlorate of Potash, Antipyrin, Carbolic acid, Naphthol and *Vicia faba*	Haemoglobinuria in Blackwater Fever and Paroxysmal Haemoglobinuria
Malaria	**Quinine**	**Blackwater Fever.**
1. Haemoglobinuria 2. Fever 3. Rigor 4. Vomiting 5. Prostration 6. Anaemia Negative.—Rarity of severe Jaundice	Resemble those of an attack of Blackwater Fever, but are not so acute. Jaundice slight or absent.	1. Haemoglobinuria 2. Fever 3. Rigor 4. Vomiting 5. Intense weakness 6. Anaemia *Additional.* (*a*) Anorexia (*b*) Headache (*c*) Pains Back and Legs (*d*) Nausea (*e*) Diarrhoea (*f*) Thirst (*g*) Constipation (*h*) Jaundice (*i*) Hyperpyrexia (*j*) Coma

also occur in the quinine and blackwater fever columns. Additional signs and symptoms are enumerated under blackwater fever, and these evidently apply also to the quinine group, since the signs and symptoms of the latter are said to resemble those of an attack of blackwater fever but are not so severe. The value of these additional signs and symptoms as a means of distinguishing the blackwater and quinine groups on the one hand from the malaria group on the other, appears to be entirely discounted by the fact that these signs and symptoms are all, without exception, adduced by the authors in their foregoing description of one or other form of the malaria infections.

In the analysis of the differential diagnosis we find ourselves reduced to the following:—

(1) In the malaria group, the rarity of severe jaundice.

(2) In the quinine group, the relative lack of severity of the symptoms and the fact that jaundice is absent or slight.

Jaundice.

The patient whose chart is given below and who died of blackwater fever presented, some weeks before the date of the commencement of the chart, slight jaundice, which passed off in a day; he had a similar slight transient jaundice a week before his fatal attack of blackwater fever. At the time of the second attack of mild jaundice he had subtertian parasites in his blood in small numbers, and he had also taken quinine irregularly. To what, then, are we to attribute these mild attacks of jaundice? To haemolysis from malaria, or quinine or blackwater fever? It appears legitimate to assume that they were a manifestation of the same causes of haemolysis as produced the marked attack of blackwater fever. It is of importance to note that in this case during the fatal attack the jaundice was not of an intense kind. Deep jaundice, again, is known to occur in malaria; in fact, many authors include the 'yellow fever-like type' of malaria in their description. One of the cardinal signs of this type is deep jaundice.

From a study of this table of differential aids, one must conclude that although it may in the future be possible to distinguish accurately between a malaria, a quinine and a blackwater haemoglobinuria, this cannot by such aids be done to-day; the attempt at differential diagnoses on such slender evidence as the degree of jaundice and the severity of the symptoms is unscientific. It is commonly stated that blackwater fever is, owing to its severity, a condition which leaves no doubt in the mind as to the diagnosis. But if blackwater fever is a disease which presents itself in an acute form, and in an acute form only, then it is, indeed, a disease *sui generis* and incomparable with any other known disease.

Stephens' views on blackwater fever are quoted by the authors: 'Blackwater is not a disease *per se*, but rather a condition of blood in which quinine, other drugs, cold or even exertion, may produce a sudden destruction of red cells. The condition is produced only by malaria, and generally by repeated slight attacks, insufficiently combated by quinine. In such cases of chronic malaria, *i.e.*, in those suffering from anaemia, with repeated attacks of fever and repeated doses of quinine, blackwater fever sooner or later almost certainly supervenes, at least in tropical climates.' The authors' comment upon Stephens' account is as follows:—'These statements are too

sweeping if genuine blackwater is meant, otherwise the home of the disease would be Ceylon, whereas it is so rare that we have never heard of a genuine non-imported case; for in this island there are Europeans and natives with just the conditions required by Stephens, and yet they do not develop blackwater fever, because the only two cases which we have met with or heard of in Ceylon in twelve years were most probably cases of quinine haemoglobinuria. On the other hand, Stephens' remarks are correct if applied to quinine haemoglobinuria.' The last sentence of this criticism is important. If it be a fact that in Ceylon there are Europeans and natives with just the conditions required by Stephens, and if it be a fact that Stephens' remarks are correct if applied to quinine haemoglobinuria, how are we to explain the low prevalence of quinine haemoglobinuria in Ceylon, *i.e.*, two cases in twelve years?

The observation was made in this case of the occurrence of transient jaundice on two occasions before the severe attack of blackwater fever, malaria parasites being present on the second occasion; these preliminary attacks of jaundice may have represented the occurrence in the blood of—in a less degree—the same changes produced by the same cause as was active during the attack. The probability of such mild haemolytic attacks is great and they are easily overlooked by the patient, as they were in this case. It is also unlikely that anything short of a severe attack will attract the attention of the patient to his urine, and if the attention is not drawn to the urine, it is certain that under the conditions of life in such places as Africa a person will frequently fail to notice that his urine is abnormal. In order to observe even considerable degrees of haemoglobinuria, it is necessary to examine the urine in a suitable vessel in a good light, precautions not usually possible for patients living under the conditions which prevail in places where blackwater fever occurs. I would suggest, then, that closer investigation will reveal the fact that haemoglobinuria occurs frequently in the tropics without being observed, and that still more frequently haemolysis with slight jaundice occur without noticeable haemoglobinuria, and that these conditions are in fact frequently due to the same causes as blackwater fever and are mild forms of the same condition. Even in England, one has seen a case who was walking about and was unaware of the fact that he was passing haemoglobin in the urine in quite noticeable quantity.

Short of 'blackwater' fever, which represents a gross haemoglobinuria, there must be many degrees of haemolysis, haemoglobinaemia and slight haemoglobinuria produced by exactly the same agencies as produce 'blackwater.' For such cases I would suggest that the term 'blackwater' fever is not sufficiently comprehensive. We require a term for such conditions to indicate that the process of haemolysis has not produced such a degree of haemoglobinaemia as to result in the passage of haemoglobin in the urine.

Numerous suggestions as to the nature of the causal parasite of blackwater fever have been made during the last thirty years. Protozoa, bacteria, spirochaetes and chlamydozoa are represented among the suggested parasites. The suggestion of Sambon that blackwater fever might be due to a piroplasma-like parasite has been accepted by some, and there are many points of resemblance between this condition in man and piroplasmosis in animals. Dudgeon (1920) injected sterilized urine from cases of blackwater fever—obtained during the period of haemoglobinuria—into animals, without producing any ill-effects. This observer mentions as a possibility that the disease may be caused by a filter passer.

Experimental Inoculation of Blackwater Fever Blood

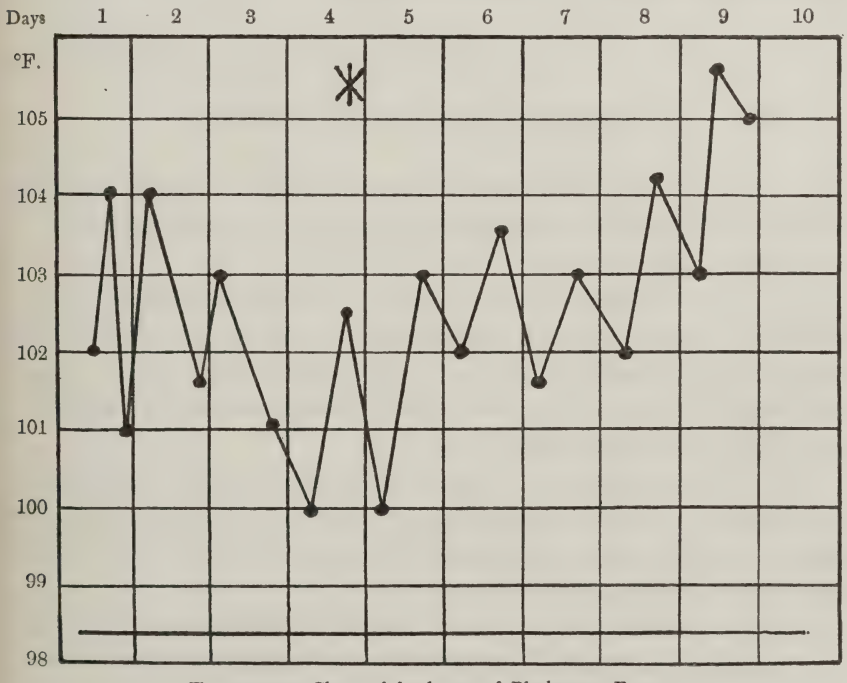
In order to throw some light upon this important question of whether or not there is a specific parasite or enzyme which causes blackwater fever, an experimental inoculation was performed. Blood was taken from the patient in the middle of what proved to be a fatal attack of blackwater fever, and was injected into a healthy European. The blood was withdrawn from a vein in the arm into a syringe containing citrated saline solution (2 per cent. Sod. cit. and 0·85 per cent. Sod. chloride, equal parts) and was injected in two portions into the recipient. The proportion of blood to citrate saline solution was three to one, and of this about 10 minims was injected deep into the region over the deltoid muscle at 3.45 p.m. and 2 c.c. into the same region at 4 p.m. The recipient had previously had malaria, the last infection being of the subtertian variety, but he had been free from relapse for over eighteen months and had taken no quinine for over eight months.

There was no local or general reaction immediately following the injections. Quinine bihydrochloride was administered orally in order to obviate infection with malaria. The dates, times and doses were as follows:—

December 4	...	10 grs.	...	4 p.m.
	...	5 grs.	...	8 p.m.
	...	5 grs.	...	10 p.m.
December 5	...	5 grs.	...	9 a.m.
	...	5 grs.	...	1 p.m.
		30 grs.		in 21 hours.

It might be argued that the doses of quinine taken might be capable of killing the parasite causing blackwater fever. Against this we have the record of numerous cases of blackwater fever in which even large doses of quinine failed to abate or ameliorate the condition. Also in the fatal case in question, quinine was administered by intramuscular injection on the sixth and seventh days of the disease, 21 grains in all, without influencing the temperature or improving the general condition.

Appended is the chart of the case giving the highest and lowest temperatures recorded each day. It will be observed that at the



Temperature Chart of fatal case of Blackwater Fever.

* Time at which injection was made.

time of injection the temperature of this patient was over 102° F., and that it remained high till his death five days later. It seems likely that if there was an infective agent it should have been present in the blood on the day of inoculation. Sources of fallacy include the possibility that the parasite of blackwater fever is never present in the blood at all; that it is present in such small numbers that the amount injected did not include the organism; that the parasite is present only for one or two days at the commencement of the disease; that it has an unusually long incubation period; or that the subject of inoculation was immune.

Result of inoculation

No immediate nor late effects were noted as the result of the inoculation. Parasites were not found in the blood, nor was there any rise of temperature nor haemoglobinuria observable during a period of two months.

These facts appear to me to militate against the specific parasitic theory of the etiology of blackwater fever.

SUMMARY AND CONCLUSIONS

1. The term 'Blackwater' Fever, being applicable only to conditions in which haemoglobin is present in visible quantity in the urine, is too restricted.

2. The importance of pre- and post-haemoglobinuria states which are inherent parts of the disease, is apt to be lost sight of owing to the exclusive use of the term 'Blackwater' Fever. Some such term as 'Occult' or 'Subliminal' Blackwater Fever might be used to express these conditions.

3. A differentiation of Tropical Haemoglobinurias into Malaria, Quinine and specific Blackwater types is not possible merely on the basis of the presence and degree of jaundice, or on the relative severity of the signs or symptoms.

4. The existence of a parasitic cause of Blackwater Fever has been frequently suggested; an experimental human inoculation, with

blood from a severe case of Blackwater Fever which ended fatally, elicited no evidence in favour of the existence of such a parasite after an observation period of two months.

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